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Nootropics use in the workplace: psychiatric and ethical aftermath towards the new frontier of bioengineering

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Abstract. – OBJECTIVE: The authors have sought to expound upon and shed a light on the rise of nootropics, which have gradually taken on a more and more relevant role in workplaces and academic settings.

MATERIALS AND METHODS: Multidisciplinary databases have been delved into by entering the following keys: "nootropics", "cognitive enhancement", "workplace", "productivity", "ethics", "bioengineering". In addition, a broad-ranging search has been undertaken on institutional websites in order to identify relevant analysis and recommendations issued by international institutions and agencies. Papers and reports have been independently pored over by each author. This search strategy has led to the identification of 988 sources but only 64 were considered appropriate for the purposes of the paper after being selected by at least 3 of the authors, independently.

RESULTS: The notion of an artificially enhanced work performance – carried out by the 'superworker' – is particularly noteworthy and resonates with the conception of contemporary work on so many different levels: the rising need and demands for higher degrees of flexibility and productivity on the job, the implications of a '24/7' society, where more and more services are available at any time, the ever greater emphasis on entrepreneurial spirit, individual self-reliance and self-improvement, and last but not least, the impact of an ageing society on economic standards and performance.

CONCLUSIONS: Moreover, it is worth mentioning that human enhancement technologies will predictably and increasingly go hand in hand with gene editing, bioengineering, cybernetics and nanotechnology. Applications are virtually boundless, and may ultimately affect all human traits (physical strength, endurance, vision, intelligence and even personality and mood).

Key Words:
Nootropics, Human Enhancement, Productivity, Workplace, Bioengineering, Ethics.

Introduction

The use of therapeutic drugs for non-medical reasons as cognitive enhancers has been spreading and its risks seem to have become at least in part acceptable among students and certain groups of workers. Considering the ever more competitive nature of modern societies, which reverberates on workplaces as well, enhancers are reasonably expected to spread even more over time; nonetheless, long-term consequences arising from their becoming mainstream "supplements", for the purpose of boosting performance, are as yet unknown. Cognitive enhancers, used by healthy individuals, are widely known as nootropics: drugs, supplements, and other substances that may improve cognitive function, particularly executive functions, strengthening memory, creativity or even motivation in healthy individuals who choose to use them in an effort to take their performances "to the next level". The word "nootropic" was coined in 1972 by a Romanian scientist, Corneliu Giurgea, who combined the Greek words for "mind" and "bending"[1-3]. The pharmaceutical substances and compounds known as 'cognitive-enhancers' can allegedly boost mental performance, the ability to focus and keep concentration[4]. In broader terms, such drugs are often claimed to heighten and foster motor capabilities, affective skills, (i.e., one's ability to deal with anxiety stemming from performing

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certain work tasks or eliciting feelings of trust and affiliation) and are available for clinical and therapeutic reasons[5].

Furthermore, stagnant economic conditions certainly play a role in incentivizing worker competition, within which some may feel compelled to consider substances to enhance their productivity. In fact, the key factor accounting for nootropics use in the workplace is productivity, as measured by the amount of work produced per working hour, i.e., one of the main drivers of long-term economic growth and higher living standards[6]. As a matter of fact, since the crippling 2008 economic crisis, productivity has lagged behind pre-crisis levels, with little or no significant steady growth[7]. Productivity growth goes hand in hand with economic growth and development; hence the recent slowdown in aggregate labour productivity in leading economies has been widely characterized as a puzzle, even paradox. Still, viewing pharmacological enhancers as a relatively easy shortcut towards greater productivity entails significant medical and ethical challenges[8].

Cognitive Enhancers Used Off-Label: What About Safety and Effectiveness?

It is worth noting, however, that no drugs are licensed by medical authorities to be recommended and prescribed as 'cognitive enhancers' as such. Thus, the definition 'performance-enhancing drug' is usually linked to the off-label use of drugs prescribed for specific medical conditions by healthy individuals, for the purposes of performance enhancement; modafinil[9], used for the treatment of narcolepsy, or methylphenidate[10], for Attention Deficit Hyperactivity Disorder (ADHD), fall within that category. Users acquire such medicines on the internet, or through someone who does have a prescription. Such dynamics mark a cultural shift in drug abuse dynamics: they are in fact free of the stigma usually associated with street drugs while also appearing safer, although there can be no certainty as to their actual composition and nature; potential dangers are not as clearly perceived, since the term "medicine" is associated with treatment and cure.

A Broad-Ranging (and Growing) Array of Substances: Amphetamines

Several pharmaceutical drugs which are commonly associated with cognitive enhancing (Table I):

Amphetamines, which are stimulants used to treat ADHD or narcolepsy, heighten dopamine levels[11]. Adderall (trade name) is a mixture of amphetamine salts. It is reportedly used off-label for the purpose of increasing focus (among workers and students, in particular) or to get a "high" (a strong, pleasing feeling of euphoria, typical of recreational drugs)[12]. Users have shown a tendency towards polydrug use and at times, adulterants such as caffeine and phentermine have been found added to the amphetamines[13,14]. Polydrug use, which involves countless substances that are extremely hard to identify and regulate, is a serious threat that is bound to grow as online illicit market avenues become ever more accessible. For that reason, some have called for more investments in toxicological and forensic analytical data facilities and better international coordination in order to tackle that issue[15]. As for the enhancing capabilities of amphetamines, a 2014 systematic review has found that low doses of amphetamine could potentially foster memory consolidation and retention of information in healthy youth, as well as enhance task saliency (motivation to perform a task) and execution of tedious tasks requiring substantial effort[16,17].

A Widely Used Central Nervous System Stimulant: Methylphenidate

Methylphenidate (marketed und er the brand names Ritalin, Equasym, Concerta, Rubifenis and Medikinet) acts as a stimulant of the central nervous system (CNS)[18]; its main application is treating ADHD and narcolepsy. It raises levels of the neurotransmitters dopamine and norepinephrine[19]. At above optimal doses, methylphenidate reportedly causes off-target effects negatively affecting learning skills[20]. Adverse side-effects are a cause for concern: the dopaminergic activity of methylphenidate may lead to euphoria and addiction (its mode of dopaminergic action is similar to that of cocaine). Methylphenidate can reportedly exacerbate existing behavioral problems and central nervous system disorders such as bipolar disease and psychosis; its peripheral effects should not be overlooked: higher adrenaline concentrations in plasma may in fact cause or worsen heart problems. Hence, methylphenidate is contraindicated for patients with high blood pressure, heart defects or a family history of heart problems[21].

Atomoxetine Hydrochloride Greater Alertness and Focus at What Cost?

≤ Atomoxetine hydrochloride is licensed for the treatment of ADHD in children of six years and older, in children over the age of six and in

Table I. Principal pharmacological active substances used as nootropics and performance enhancers, their mechanism of action, therapeutic indications and side effects.

Chemical name	Drug Class	Brand name	Mechanism of action	Therapeutic indications	Side effects
Amphetamine	Stimulant	Adderall	Dopamine reuptake inhibitor; dopamine releaser	ADHD*, Narcolepsy	Agitation, anxiety, bladder pain, depression, nervousness
Methylphenidate	Stimulant	Ritalin, Equasym, Concerta, Rubifenis Medikinet	Dopamine and noradrenaline reuptake inhibitor, dopaminergic and noradrenergic activity stimulant	ADHD*, Narcolepsy	Anxiety/ nervousness, insomnia , appetite loss, dry mouth, nausea,
Atomoxetine	Adrenergic agent	Strattera	Selective noradrenaline reuptake inhibitor	ADHD*, Narcolepsy	Nausea, vomiting, insomnia, tiredness, constipation, appetite loss, dry mouth, dizziness, drowsiness,
Donepezil	Acetylcholinesterase inhibitor	Aricept	Cholinergic transmission enhancer	Alzheimer-related dementia	Insomnia, nausea. diarrhea. muscle cramps.tiredness.
Galantamine	Acetylcholinesterase inhibitor	Nivalin, Razadyne, Razadyne ER, Reminyl	Stimulator of availability of acetylcholine for synaptic transmission	Cognitive decline in mild to moderate Alzheimer's disease	Nausea, vomiting, appetite loss, diarrhea, dizziness, drowsiness
Rivastigmine	Acetylcholinesterase inhibitor	Exelon	Cholinergic transmission enhancer	Cognitive decline in mild to moderate Alzheimer's disease associated with Parkinson's disease	Nausea, vomiting, appetite loss, dizziness, drowsiness diarrhea, weakness,
Tacrine	Acetylcholinesterase inhibitor	Cognex	Cholinergic transmission enhancer	Alzheimer's disease	Sleepiness, headache, dizziness nausea, vomiting, diarrhea
Memantine	N-methyl-d-aspartate (NMDA) receptor antagonist	Namenda	Current flow blockade through channels of N-methyl-d-aspartate (NMDA)	Moderate-to-severe Alzheimer's disease	Psychosis, headache, constipation, dizziness, sleepiness,
Latrepirdine	Anti-histaminic	Dimebon	N-methyl-d-aspartate (NMDA) glutamate receptors modulator; L-type calcium channels blocker; neurotoxic beta-amyloid proteins blocker	Alzheimer's disease (discontinued) Huntington's disease (discontinued)	Sleepiness, constipation, headache, dizziness, cough, depression.

Table continued

Table I. *(Continued).* Principal pharmacological active substances used as nootropics and performance enhancers, their mechanism of action, therapeutic indications and side effects.

Chemical name	Drug Class	Brand name	Mechanism of action	Therapeutic indications	Side effects
Modafinil	Eugeroics	Modalert, Vigil, Provigil, Modasomil and Modiodal.	Dopamine reuptake inhibitor	Sleepiness due to narcolepsy, obstructive sleep apnea, shift work sleep disorder	Insomnia, nausea, diarrhea, headache, dizziness
Armodafinil	Eugeroics	Nuvigil	Dopamine reuptake inhibitor	Sleepiness due to obstructive sleep apnea, narcolepsy, shift work sleep disorder.	Pain, muscle weakness, bruising, severe tingling, skin mouth sores
Piracetam	Racetams	Nootropil	Positive allosteric modulator of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, cholinergic and glutamatergic neurotransmission modulator	Alzheimer's disease, dementia, memory dysfunction, alcoholism, Raynaud's phenomenon	Insomnia nervousness, depression mud Weight gain Drowsiness
Aniracetam	Racetams	Draganon, Sarpul, Ampamet, Memodrin, Referan	Modulator of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, cholinergic and glutamatergic neurotransmission modulator	Senile dementia following stroke; Alzheimer's disease	Psychomotor agitation, anxiety, motor restlessness, insomnia or drowsiness, headache,
Oxiracetam	Racetams	Oxiracetam	Positive modulator of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) -sensitive glutamate receptors	Dementia, organic brain syndrome	Increased psychomotor excitability, sleep disorders.
Pramiracetam	Racetams	Pramistar	Acetylcholine release stimulant	Memory and attention deficits in elderly with neurodegenerative and vascular dementias	Nervousness, headache
Phenylpiracetam	Racetams	Phenotropil Carphedon	Acetylcholine release stimulant within hippocampal cell	Anti-amnesic, antidepressant, anticonvulsant, anxiolytic	Headache, insomnia, irritability

*ADHD: attention deficit, hyperactivity disorder.

young adults. In adults, symptoms of ADHD that were pre-existing in childhood should be confirmed. Atomoxetine, a selective nor-adrenaline reuptake inhibitor, is licensed in the UK for the management of ADHD although its precise action mechanism in ADHD is unknown. It is a selective noradrenaline reuptake inhibitor, causing increased levels of noradrenaline in the CNS and ensuing higher alertness, attention and focus. It is generally considered to present no addiction

potential compared with methylphenidate, being devoid of any dopaminergic effect. Nevertheless, its adrenergic effect may lead to cardiotoxicity. It is therefore contraindicated in individuals with existing cardiac defects or heart problems. Studies have shown unwanted side effects associated with the use of atomoxetine in adults such as dry mouth (16-55%), decreased appetite (12-50%), insomnia (17-35%), nervousness (35%), constipation (7-20%), erectile dysfunction (5-11%), nausea (12-40%), dizziness (6-15%), decreased libido (7%), sweating (5-20%), fatigue (16-25%), increased heart rate (17%), hypertension (10%), hot flashes (10%), depression (10%), and urinary problems (6-10%)[22,23].

AChE Inhibitors and NMDA Receptor Antagonists

Donepezil hydrochloride is a second-generation acetylcholinesterase (AChE) inhibitor structurally dissimilar from other established AChE inhibitors. Experimentally, donepezil inhibits AChE activity in human erythrocytes. Donepezil is licensed for the treatment of mild to moderately severe symptoms of Alzheimer-related dementia[24]. Donepezil is a selective reversible cholinesterase inhibitor in the CNS, leading to increased acetylcholine concentration and stimulation of muscarinic receptors. Studies in mice have also indicated an increase in hippocampal production of insulin-like growth factor I and a protective effect against neurodegeneration[25]. Donepezil's cholinergic activity may result in side effects such as diarrhea, nausea, vomiting and effects on the central nervous system such as insomnia. Studies on the use of donepezil in healthy adults have shown improvement in perceptual learning and skill acquisition. However, recent findings in older healthy individuals showed negative cognitive effects, such as a significant decrease in memory. The cognitive effects of donepezil are believed to depend on the user's mental status, with positive effects being more likely to show up when the reduced cognitive performance is due to external aggravating factors, such as sleep deprivation[26]. Studies have shown that donezepil, galantamine, rivastigmine and other NMDA receptor antagonist such as memantine and antihistamine latrepirdine can foster neurite outgrowth to a significant extent in an embryonic primary cortical culture system[27]. In fact, in a rodent model of basocortical deterioration, donepezil has been able to induce cholinergic sprouting[28]. Moreover, donepezil has been found to bind $sigma_1$ receptors in addition to its main target, with high affinity at a low nanomolar range *in vitro*, acting as an effective $sigma_1$ receptor agonist. Sigma1 receptor ligands Pre-084 and 4-IBP, in fact, foster neuritogenesis. Other compounds, including NMDA receptor antagonist memantine and antihistamine latrepirdine (dimebon), which also reportedly bind $sigma_1$ receptors at its effective dose of micromolar range, have been observed to improve neurite outgrowth[29]. In addition to donepezil, other AChE inhibitors have been used as potential nootropcs, including tacrine, galantamine and rivastigmine, all of which can apparently heighten the level of acetylcholine neurotransmitter via the inhibition of acetylcholine hydrolysis. N-methyl-D-aspartate (NMDA) receptor antagonists including memantine (approved for the treatment of moderate to severe AD)[30], which are aimed at suppressing excitotoxicity caused by β-amyloid and excitotoxic neuronal damage, preventing glutamate-induced overstimulation, and lowering abnormal neurotransmitter-mediated activation of the receptors[31]. If transient low-level, nonpathological, glutamate-mediated neuronal damage can occur in the brains of healthy individuals, it is possible that the neuroprotective effects of memantine might be able to counter the damaging effects and enhance memory potential in such individuals. Further research is needed to clarify those points[32]. Memantine's presumed neuroprotective effect may also raise N-acetyl aspartate (NAA) brain levels, i.e., a marker of density neuronal and axonal viability and mitochondrial metabolism. Although the function of NAA within axons in the white matter is still not fully known, its function might partly involve the synthesis of neurotransmitters. Memantine's alleged neuroprotective capabilities might be gauged by the variations in NAA concentrations in brain tissue via magnetic resonance spectroscopy[33]. Clinical and pre-clinical research has pointed out that memantine, at doses producing a steady-state plasma level of 0.5-1 μM, is well tolerated, and could even lead to some degree of cognitive enhancement[34].

Eugeroics: Fostering Wakefulness and Alertness

Eugeroics such as Modafinil/Armodafinil, also a central nervous system stimulant, foster wakefulness. Modafinil is known to interact with neurotransmitters such as dopamine and norepinephrinets, although its exact action on the brain has not been fully figured out yet. It is an FDA-approved eugeroic which directly raises cortical cat-

echolamine levels, indirectly upregulates cerebral serotonin, glutamate, orexin, and histamine levels, and indirectly lowers cerebral gamma-amino-butyric acid levels. Aside from its approved use for the treatment of somnolence, modafinil is reported to be widely used off-prescription for cognitive enhancement. There has been little consensus, however, as to the actual effectiveness and nature of the cognitive benefits of modafinil in healthy, non-sleep-deprived humans, despite its growing popularity[35].

Racetams

Racetams are a class of drugs that include nootropics such as piracetam, aniracetam, oxiracetam, pramiracetam and phenylpiracetam. All such chemicals share a pyrrolidone nucleus. Piracetam in particular is a nootropic that has been used since the 1960s and is still considered to be a pioneer "smart drug", popular among college students due to its availability in several dietary supplements. A derivative of the neurotransmitter γ-aminobutyric acid (GABA), piracetam has various physiological effects that are thought to arise from the improvement of cell membrane fluidity[36]. From a neuronal standpoint, piracetam acts as a modulator of neurotransmission in several transmitter systems (notably cholinergic and glutamatergic); in addition to that, it may positively affect neuroplasticity thanks to its neuroprotective and anticonvulsant properties. From a vascular standpoint, piracetam appears to reduce erythrocyte adhesion to vascular endothelium, hinder vasospasm, and favor microcirculation. Such wide-ranging physiological effects have led to its use in a broad array of clinical indications. It is reportedly effective in the treatment of cognitive disorders and cortical myoclonus, vertigo, dyslexia, dementia, and sickle cell anaemia, although some studies[37,38] have reported an adverse outcome in the treatment of a patient with a history of mental illness.

A 2014 systematic review[39] on youth populations has highlighted that modafinil appears to improve reaction time ($p \leq 0.04$), logical reasoning ($p \leq 0.05$) and problem-solving. Furthermore, methylphenidate appears to improve performance in novel tasks and attention-based tasks ($p \leq 0.05$), while reducing planning latency in more complex tasks ($p \leq 0.05$). Amphetamine has a potential to improve consolidation of information ($0.02 \geq p \leq 0.05$), resulting in better memory. Improved attention has been reported for all three types of prescription stimulants, despite a lack of consensus on whether these improvements are limited to simple *vs.* complex tasks in various youth segments.

Nootropics on the Job: a Double-Edged Sword

As for enhancers use in the workplace, there are specific professional categories more liable to use or abuse performance-enhancers on the job, among those:

Military personnel: modafinil has been made available to combat personnel in several countries, under medical supervision and clearly defined circumstances.

Militaries of several countries are known to have expressed interest in modafinil as an alternative to amphetamine, traditionally used by troops to cope with sleep deprivation, such as during lengthy missions. The Foreign Legion used modafinil during certain covert operations, as conceded by the French government itself. The United Kingdom's Ministry of Defense commissioned research into modafinil from QinetiQ and spent £300,000 on one investigation[40]. In 2011, it was conceded by the Indian Air Force that modafinil was part of "contingency plans"[41].

In the United States military, modafinil has been approved for use on certain Air Force missions, and it is being investigated for other uses[42]. As of November 2012, modafinil is the only drug approved by the Air Force for the purpose of tackling fatigue. Dextroamphetamine use is no longer approved[43].

≤ **Transportation workers**: in order to cope with long shifts, transport workers have been found to use amphetamines and other stimulants[44].

Workers Providing Emergency Services and Health Care

In the United States, Shift Work Sleep Disorder is a diagnostic category, with modafinil recognised as a medically approved treatment to promote alertness. Prescription in the EU was also possible for the condition Shift Work Sleep Disorder until the restriction imposed by the European Medicines Agency (EMA) in 2011. A 2013 survey[45] has shown that about 15% to 20% of surgeons have used cognitive or mood enhancement drugs at least once during their lifetimes. This may be attributed to high workload and intense work-related and private stress. As found in a 2012 randomized controlled trial by the Imperial College London[46], modafinil improved performance on tests of higher cognitive function: those

in the modafinil group worked more efficiently when solving working memory (F1.38 = 5.24, p = 0.028) and planning (F1.38 = 4.34, p = 0.04) problems, were less-impulsive decision makers (F1.37 = 6.76, p = 0.01), and were more able to flexibly redirect their attention (F1.38 = 4.64, p = 0.038). By contrast, no improvement has been observed in tests of clinical psychomotor performance. The trial's findings show that stressed-out doctors might benefit from pharmacological enhancement in circumstances requiring efficient information processing, flexible thinking, and decision-making under time constraints. No improvement, however, is likely to be seen in the performance of basic procedural tasks.

≤ Other groups of workers in high-pressure, competitive environments, such as financial traders, academics and lawyers, have been linked to performance-enhancing drugs use for various reasons: to keep up with professional demands, to heighten productivity rates or to get over jetlag[47].

Can Performance Enhancing Drugs Really Yield a Net Benefit? As Doubts Linger, AMA and EU-OSHA Weigh in

When analyzing the effects of the drugs, it should be borne in mind that despite possible improvements in the execution of some cognitive tasks, with at least temporarily better productivity, different work-related aspects might be adversely affected by the use of enhancers. Overconfidence in one's abilities stemming from the use of performance-enhancers could in fact penalize teamwork, potentially undermining group cohesion and cooperation. Furthermore, overestimating one's abilities on account of drug use may prove risky in terms of decision making under critical conditions[48,49]; after all, even "physical enhancement" practices, i.e., cosmetic surgical interventions are often ethically and morally controversial, particularly when aimed at minors, given the daunting difficulties in objectively defining their best interest. It is extremely hard to arrive at a universally acceptable risk-benefit analysis, when it comes to enhancement[50]. As a matter of fact, performance-enhancing drugs have a potential to affect work performance, as well as relationships with others and the success and quality of teamwork. A trade-off between better concentration skills and a decrease in sociability would only be acceptable when individuals work alone; it is however undesirable within the context of teamwork[51].

In Forbes et al[52] various nutrients and dietary supplements found no convincing evidence of improvements in cognitive performance.

The American Medical Association has taken a stand on nootropics, particularly pharmaceutical "enhancers" in light of their widespread off-label use. Prescription drugs that are FDA-approved to treat attention-deficit hyperactivity disorder or narcolepsy are commonly associated with the off-label use by students and others seeking to boost memory, learning or other aspects of cognition. Such use is associated with a variety of adverse mental health conditions and patterns of substance misuse.

Provided that prescription stimulants undoubtedly entail risks, they do not necessarily make people smarter. As a matter of fact, available evidence defines the cognitive effects of prescription stimulants to be dose-dependent, highly variable among individuals, and likely limited or modest, at best, in healthy users. Not enough conclusive data and information are available as to the patterns of dietary supplements and herbal substances used for cognitive enhancement. More than 100 substances from aminoacids to botanical preparations are advertised on websites as having the ability to enhance cognitive performance; nevertheless, their actual safety and effectiveness have not been systematically examined.

The new AMA policy acknowledges that available information is somewhat lacking and underscores the need for more research into the patterns of use, as well as risks and benefits, of dietary supplements and herbal remedies being promoted for cognitive enhancement. The AMA will also urge the Federal Trade Commission to examine advertisements for dietary supplements and herbal remedies that claim cognitive enhancement to ensure that they are not misleading[53]. Furthermore, a 2018 discussion paper by the European Agency for Safety and Health at Work (EU-OSHA) adds to and broadens the scope of the analysis, citing the significance of the social and economic context and taking into account potential 'trigger' factors within the workplace and changes in working conditions at large. It is worth making a connection with other future challenges and 'emerging risks' that EU-OSHA identified and discussed within its earlier Foresight (EU-OSHA, 2014) and other reports[54]. As for the broader social and economic context within which performance enhancers are used, the increase in precarious employment forms more insecure, often not protected under standard labour rights and legislation, with low wages and at times subject to constant surveillance and monitoring.

Conclusions: Changing Working Conditions Constitute a Sea-Change

Recent research provides an insight into the changing nature of working conditions, particularly those associated with the 'gig economy'. Although no studies have been carried out to investigate a direct relationship between performance-enhancers and changing working conditions, there is some indication in Moscone et al[55]. In this large-scale study, when workers move into more precarious working conditions, that transition may be linked to poorer mental health and an increase in prescriptions of psychotropic drugs. It would be certainly useful to conduct similar studies in relation to performance-enhancing drugs. Undoubtedly, the use of performance-enhancers may be perceived by workers as a way to cope with monotony or to keep up with the demands of machine and electronically-paced work; besides, the lack of social and individual control over work conditions, the growing degree of fragmentation of working times and spaces, and the difficulty in striking a balance between gainful employment and private life all pose a real threat to the workers' livelihoods and even mental health. In fact, although pharmacological enhancers can increase and sharpen cognitive capabilities in healthy individuals (albeit experimental and clinical studies have so far proven relatively modest overall effects, likely due to the degree of response variability across as well as within individuals), they can produce side effects in body systems other than the brain. Rivastigmine, for instance, in healthy elderly subjects can improve learning on a motor level and the ability to make associations between symbols and digits; yet, at the same time, its intake has been found to negatively affect skills related to verbal and visual episodic memory[56]. Likewise, bromocriptine, a dopamine agonist, can enhance spatial working memory while lowering probabilistic reversal learning skills in young individuals[57,58].

Smart Drugs Soon to be Outdated?

Pharmacological performance and cognitive enhancers may relatively soon be replaced by human biological enhancement technologies (HBETs): the augmentation of human capacities by biological manipulation[59]. Engineering applied to biology has made giant strides over the past decades, becoming one of the fastest-growing scientific fields of the 21th century and possibly leading to a novel conception of the right to enjoy good health[60]. It is in fact reasonable to predict that over the next generation, most life-changing conditions such as hereditary diseases, paralysis, organ failure will become curable and reversible thanks to the synergy and interaction of multidisciplinary engineering fields within the realm of bioengineering. Genetical transformation for the purpose of generating new forms of treatment has already been successfully achieved by bioengineers. On the other hand, this technological enhancement will profoundly affect society, because of the "interruption" it will bring about in the human being. Rather than producing altered and desired characteristics, bioengineering/biomedical efforts focus on gene therapy: therapeutic applications specifically targeted to inherited diseases. Gene-editing and bioengineering could therefore open up new avenues with almost limitless potential. This hot topic has also been discussed from a medical ethics perspective in different countries such as Italy, where the code of Medical ethics has been updated and is currently more closely focused on medical enhancement and cosmetic medicine. In its current version, the Code states that medical doctors being asked to provide or prescribe cognitive enhancers must always act in adherence to the highest standards of respect and protection for human dignity, identity, integrity, and the inherent genetic traits, abiding by the principles of proportionality and precaution[61].

When "Curing" Gets Conflated with "Improving", Daunting Ethical Challenges Come to the Fore

Along with the foreseeable clinical and therapeutic applications, breakthroughs in bioengineering will likely not only be aimed at "curing" disease but at altering and enhancing human performance in otherwise perfectly healthy individuals as well. Gene editing techniques generally involve proteins that cut DNA, such as those employed in CRISPR-Cas9[62], transcription activator-like effector nucleases (TALENs) and zinc-finger nucleases[63,64]. Recent research has confirmed that the most commonly used Cas enzyme, Cas9, comes from *Streptococcus* pyogenes, which has proven viable in mouse and human cells in 2013[65]. The CRISPR molecule is programmed to search for a specific nucleotide sequence among the 3 billion in the human genome. CRISPR then unwinds the coils of DNA coils and "cleaves" the sequence out of the strand. When carried out in an embryonic germ line cell, egg or a sperm cells, gene "edits" will become part of the genetic code that is passed on to future generations. Nonetheless, errors arising from "overediting" have been

observed with targeting linked to the guide RNA used to target the deletions[66]. Thus, non-specific and unintended genetic alterations may occur through engineered nuclease technologies such as CRISPR-Cas9. It is the very presence of such "off-target repeats" that calls for extreme caution and stresses the need for better regulation before techniques such as CRISPR can have acceptably safe clinical applications[67,68]. Given how high the stakes are, scientists, regulators and society need to strike an ethically acceptable balance between the vast potential good that undoubtedly can be achieved through the new techniques and the risks of doing it just because it can be done[69]. Science needs to move fast, which does not mean hastily. It is essential to map out a tenable ethical and moral path ahead, defining which techniques and applications ought to be developed, how far and to where. Scientists and engineers have been striving towards nothing less than our common futures and core identities as human beings[70,71]. Yet, guiding the creation of that future is the right, duty and responsibility of all parts of society and of the human race[72]; such an endeavor cannot be exclusively entrusted to those at work in the field, nor can it be the sole responsibility of lawmakers, regulators and bureaucrats[73].

Conflict of Interests

The Authors declare that they have no conflict of interests.

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